UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,517	02/10/2000	MARCOS DA SILVA FREIRE	3673-2	6833

7590 02/22/2002

NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
ZEMAN, ROBERT	
ART UNIT	PAPER NUMBER
1645	4

DATE MAILED: 02/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,517	DA SILVA FREIRE ET AL.	
	Examiner	Art Unit	
	Robert A Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *42-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on 11-30-2001 is acknowledged. Claims 1-41 have been canceled. Claims 42-70 have been added.

New Claim Objections

Claims 42-70 are objected to because of the following informalities: All claims should be introduced with an article. Independent claims should start with either "A" or "An" while dependent claims should begin with the article "The". Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 1 and 30 under 35 U.S.C. 112, second paragraph, for being rendered vague and indefinite by their use of the phrase "once or more times" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 1 and 30 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by their use of the phrase "optionally, removing cell debris and whole cells from **the** harvested virus" is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 2 and 31 for reciting improper Markush language is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 11 and 38 as being rendered vague and indefinite by the use of the term "wild" is withdrawn. Cancellation of said claims has rendered the rejection moot

The rejection of claims 15 and 41 as being rendered vague and indefinite by the use of the phrase "YF17D strain **and** substrains thereof" is withdrawn. Cancellation of said claims has rendered the rejection moot.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-60 are rejected under 35 U.S.C. 112, second paragraph, for the reasons outlined in the previous Office Action in the rejection of claims 1-15 and 30-41. Said claims are confusing and filled with multiple errors some of which are described below. It is suggested that the claims, as a whole, be rewritten in accordance with U.S practice.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 for being rendered vague and indefinite by their use of the phrase "acceptable as a substrate for vaccine production".

Applicant argues:

1. The term "acceptable substrate" is routinely used in the art and is defined on page 30 of the specification.

2. An "an acceptable substrate" is any cell which may be used for vaccine production and is incapable of transferring genes.

3. Said term is used in U.S. Patent 6,306,637.

Applicant's arguments have been fully considered and are deemed unpersuasive.

With regard to Applicant's assertion that the term is defined on page 30 of the specification, Applicant should not e that said passage does not define said term but merely recites it.

With regard to Applicants assertion that said is recited in the claims of U.S Patent 6,306,637, said term is not recited. Said claims recite the term "cell substrate" not "suitable substrate". Additionally, applicant's arguments are based on features (i.e., a suitable substrate is a cell culture that cannot transfer genes) are not recited in the rejected claim(s).

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 for being rendered vague and indefinite by their use of the term "suitable medium".

Applicant argues:

1. Said term is well known by those of skill in the art
2. Said term is recited in the claims of U.S. Patent 6,194,210.

Applicant's arguments have been fully considered and deemed unpersuasive.

With regard to Applicant's assertion that said term is well know in the art, one of skill in the art would not know whether a given media would be "suitable" unless he knew what the media would be used for.

With regard to Applicant's assertion that said term is recited in the claims of U.S. Patent 6,194,210, said patent uses the term "culture medium" not "suitable medium". Additionally, said claims further recite components of said culture medium.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 for being rendered vague and indefinite by their use of the phrase "**the** cell culture". It is still unclear to which cell culture is Applicant is referring. It should be noted that Applicant did not address this rejection in his response to the previous Office action.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 for being rendered vague and indefinite by their use of the phrase "appropriate period of time".

Applicant argues:

1. Said phrase would be recognized as embracing periods of time that are appropriate for the incubation of the cell cultures.

Applicant's argument has been fully considered and deemed unpersuasive. One of skill in the art would not know what period of time would be appropriate unless they knew what the goal of a given action was.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 for being rendered vague and indefinite by their use of the phrase "harvesting of culture supernatant containing virus with or without addition of stabilizer".

Applicant argues:

1. Said phrase "**may** be understood by the specification".

2. Specification defines said phrase (page 4, second paragraph, page 10, paragraphs preceding Example 1 and Example 3.

Applicant's arguments have been fully considered and deemed unpersuasive.

With regard to Point 1, said argument verges on the nonresponsive since it doesn't address the rejection under discussion. Additionally, the passages cited by Applicant do not clarify what is meant by said phrase. It is still unclear what is meant by this phrase. Is the stabilizer optionally part of the virus containing culture supernatant or optionally added during harvesting of said supernatant?

Claim 58 is rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 as being rendered vague and indefinite by their use of the phrase "optionally, removing cell debris and whole cells from **the** harvested virus".

Applicant argues:

1. Said term does not mean that complete or integral cells are removed from the harvested virus.
2. The term "whole" means cells that are not disrupted.

Applicant's arguments have been fully considered and are deemed unpersuasive.

Since Applicant's response does not clarify the issue, it is still unclear how a whole cell is removed from a virus? Additionally, which specific virus particle is Applicant referring to? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 1 and 30 as being rendered vague and indefinite by their use of the phrase "optionally, virus inactivation"

Applicant argues:

1. Methods of virus inactivation are well known in the art.

Applicant's arguments have been fully considered and deemed to be unpersuasive.

It is unclear what is meant by this phrase since it does not entail an active step. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claims 2 and 31 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 43 and 59 as being rendered vague and indefinite by their use of the phrase are rendered vague and indefinite by the use of the phrase "submitted to viral infection".

Applicant argues:

1. Said phrase is related to the production of interferon by certain cell types that have been stimulated by exposure to a virus.

Applicant's arguments have been fully considered and deemed to be unpersuasive. It is unclear what is meant by said phrase. Does Applicant mean "subjected to viral infection"? How does a cell "submit" to a virus? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 45 and 61 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 3 and 32 as being rendered vague and indefinite by their use of the phrase are rendered vague and indefinite by the use of the phrase "any further passaged".

Applicant argues:

1. Said term would be understood by one of skill in the art.

2. Said term refers to "the culture of cells that is transfected with the virus for the first time or resulting from subsequent transfections".

Applicant's arguments have been fully considered and deemed to be unpersuasive.

Applicant's arguments are not understood. One does not transfect cells with a virus. One infects them with a virus. Additionally, contrary to Applicant's assertion that said term would be known to one of skill in the art, standard nomenclature categorizes cell cultures as either being "primary cell cultures" or "passaged cell cultures".

Claims 49, 50 and 64 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 7, 8 and 35 as being rendered vague and indefinite by their use of the phrase "culture is incubated at steps x, y and z from 12 to 72 (or 144) hours". It is unclear whether the time is a cumulative time or is applied to each step individually. As written, it is impossible to determine the metes and bounds of the claimed invention. It should be noted that Applicant did not address this rejection in his response to the last Office action.

Claims 52 and 66 are rejected under 35 U.S.C. 112, second paragraph, for the reason outlined in the previous Office action in rejecting claims 10 and 37 as being rendered vague and indefinite by their use of the phrase "acceptable as a component in parenteral products".

Applicant argues:

1. "Parenteral products" would be recognized by those of skill in the art as products that are not administered by digestive tube.

Applicant's arguments have been fully considered and are deemed unpersuasive.

It is still unclear what is meant by said phrase. What makes a component acceptable? What criteria are used to make such an evaluation? As written, it is impossible to determine the metes and bounds of the claimed invention.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42, 44-45, 49, 51-52, 54-56, 58, 60-61 and 65-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306) for the reasons outlined in the rejection of claims 1-3, 7, 9-10, 12-14, 30-32 and 36-40 in the previous Office action.

Applicant argues:

1. Barret et al. were interested in the molecular basis of attenuation and virulence of Yellow Fever virus.

2. Barret et al. passaged YF virus in HeLa cells.

3. Barret et al. repeated the experiments using monoclonal antibodies identifying changes in the viral envelope protein that may be related to viral virulence.

4. Applicant has developed an improved process to produce interferon inducing/sensitive vaccine viruses.

5. It is known by one of ordinary skill in the art of vaccine production that regardless of how a vaccine virus is obtained it must be capable of autonomous replication in the host cell.

6. Conditions and materials used in the process must be carefully monitored to avoid problems related to genetic variability, loss of immunogenicity, virus inactivation, neurovirulence, low yield in relation to virus input and contamination by extraneous agents.

7. Cells used for the production of vaccines for use in man are limited to those that are free of adventitious agents, non-tumorigenic and karyologically normal.

8. HeLa cells are not suitable for vaccine production since it was derived from a carcinoma of a human uterine cervix.

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

The instant claims are drawn to methods of virus propagation comprising incubating permissive cells with a virus of a given period of time, removing said inoculum, replenishing growth medium, incubating cells for a given period of time after which the growth medium is harvested (and subsequently replaced). The claims recite the following limitations: the virus being propagated is a wild-type Yellow fever virus or an attenuated Yellow fever virus; cells being infected produce interferon in response to viral infection; the incubation and culture time is between 12 and 144 hours (combined) and a stabilizer is used in the growth medium (FBS).

Regardless of the motivation, Barrett et al. disclose a method of attenuating wild-type Yellow fever virus by passage in HeLa cells. Said reference discloses a method for infecting monolayers of HeLa cells with wild-type/attenuated Yellow fever virus wherein said cells were incubated with said virus, washed after a incubation period and incubated at 37 degrees Celsius to allow for virus production. After 4 days the medium was removed/replaced and clarified. The resulting virus was then used to infect subsequent HeLa cell cultures.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the rejected claims recite methods for producing vaccines for use in man) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that Barret et al. propagated YF virus in order to study the molecular basis of attenuation and virulence of Yellow Fever virus, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306) for the reasons outlined in the previous Office action in rejecting claims 1-15 and 30-41.

The instant claims are drawn to methods of virus propagation comprising incubating permissive cells with a virus of a given period of time, removing said inoculum, replenishing growth medium, incubating cells for a given period of time after which the growth medium is harvested (and subsequently replaced). The instant claims recite the following limitations: the virus being propagated is a wild-type Yellow fever virus or an attenuated Yellow fever virus (specifically YF-17D); cells being infected produce interferon in response to viral infection; said cells are seeded at a density of 1×10^4-1×10^5 cells/cm^2; the incubation and culture time is between 12 and 72 hours (combined); and a stabilizer is used in the growth medium. Barrett et al. disclose a method of attenuating wild-type Yellow fever virus by passage in HeLa cells. Said reference discloses a method for infecting subconfluent monolayers of HeLa cells with wild-type/attenuated Yellow fever virus wherein said cells were incubated with said virus, washed after a incubation period and incubated at 37 degrees Celsius to allow for virus production. After

4 days the medium was removed/replaced and clarified. The resulting virus was then used to infect subsequent HeLa cell cultures. Bartlett et al. differs from the instant invention in that it does not specifically recite the use of seeding the permissive cells at 1 x 10^4-1 x 10^5 cells/cm^2 or harvesting the infected cultures within 72 hours. These differences, however, constitute an optimization of the method disclosed by Bartlett et al and would have been obvious to one of skill in the art. Additionally, the use of the YF-17D virus in lieu of the YF-Asibi virus disclosed by Bartlett et al. would be equally obvious to one of skill in the art since YF-17D is the standard strain used in vaccine production.

Applicant's arguments, discussed above, have been fully considered and are deemed to be unpersuasive.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42 and 58 are rendered vague and indefinite by the use of the phrase "cell culture of step (f)" in the recitation of step (f). Said recitation makes the claim circular in nature.

Claims 43 and 59 are rendered vague and indefinite by the use of the phrase "chicken embryo cells and mammalian cells which are interferon-producing cells when submitted to viral infection". It is unclear whether the interferon production is a characteristic of both cell types or merely the mammalian cells. As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 44 and 60 recite improper Markush language. The ultimate member of the listed group should be preceded by the conjunction "and".

Claims 52 and 66 are rendered vague and indefinite by the use of the term "human serum **albumen**". Albumen refers to "the white of an egg" (Webster's Ninth Collegiate Dictionary, 1983 page 68) and cannot be a component of human serum. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claims 57 and 70 are rendered vague and indefinite by the use of the term "YF17D and/or substrains thereof". It is unclear what limitation is being claimed. Are the cells infected with multiple strains/substrains of Yellow Fever virus simultaneously or is a single strain/substrain used? As written, it is impossible to determine the metes and bounds of the claimed invention.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donna Wortman can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman
February 21, 2002